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Efficacy and tolerability of Icatibant (Hoe 140) in patients with moderately severe chronic bronchial asthma

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Abstract

Bradykinin (BK) has been identified as a mediator in human bronchial asthma. The current phase II study was designed as a multicentered, double blinded, randomized, placebo-controlled, parallel-group pilot study to investigate the efficacy of the B_2 BK receptor antagonist Icatibant in adult patients with chronic asthma. Patients were treated t.i.d. with 900 μg or 3000 μg of nebulized Icatibant, or placebo. Treatment was for 4 weeks, followed by a 2-week placebo run-out. Icatibant was very well tolerated, and led to a dose-dependent improvement in objective pulmonary function tests (PFTs) measured by the investigators (e.g. FEV_1 and PEFR). At 3 mg t.i.d., a statistically significant difference (p < 0.01) between Icatibant and placebo of about 10% was achieved after 4 weeks of treatment for all PFTs. At 900 μg t.i.d., the improvement in PFTs was smaller. By contrast, no clinically relevant improvement in global symptom score (nor a reduction of rescue medication) was found when compared with placebo. The observed improvement in objective PFTs started between weeks one and two, gradually increased until the end of active treatment, and slowly decreased during the placebo run-out phase, suggesting an anti-inflammatory effect. No acute bronchodilator effect was found. In conclusion, Icatibant showed a profile expected for an anti-inflammatory asthma drug.

Keywords: Human asthma; Clinical study; Bradykinin antagonist; Icatibant (HOE 140)

1. Introduction

Bradykinin (BK) is an inflammatory and vasoactive nonapeptide released from kininogens by the proteolytic activity of kallikreins. It has a variety of pharmacological actions and causes vasodilatation, increase in microvascular permeability, edema, pain and smooth muscle contraction. In asthmatic subjects inhaled BK is a potent bronchoconstrictor (Fuller et al., 1987), but has no such action in healthy subjects. BK also produces dyspnea and mimics symptoms of asthma like coughing and retrosternal discomfort. Since in asthma plasma is leaked into airways and kallikrein (Christiansen et al., 1987) and bradykinin (Baumgarten et al., 1992) are found to be increased in bronchoalveolar lavage fluid, it is reasonable to assume that bradykinin may play a role in asthma. Bradykinin could contribute to airway narrowing, sensory symptoms of asthma and also inflammation of the bronchi, because it is one of the most potent inflammatory compounds. Therefore, antagonists of

Abbreviations: t.i.d.: three times daily; Bradykinin: BK; PFTs: Pulmonary function tests; FEV_1: Forced expiratory volume; PEFR: Peak expiratory flow rate; FVC: Forced vital capacity; FEF(25–75%): Mid-expiratory flow rate; MDI: Metered dose inhaler

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bradykinin like the B_2 receptor antagonist Icatibant (HOE 140) (Hock et al., 1991, Wirth et al., 1991, 1993), which is potent and long-acting in a variety of pharmacological models, might have a therapeutic potential in human asthma.

The purpose of the current study was to investigate the efficacy, safety and tolerability of inhaled Icatibant in the treatment of adult patients with chronic asthma.

2. Materials and methods

The current study was a multicentered, double blinded, randomized, placebo-controlled, parallel-group pilot study. 30 patients were recruited in 19 centers in the USA. Patients of both sexes, aged 18–65 years, with moderate to severe asthma were enrolled. The following criteria were selected as markers of severity to ensure that asthma was severe enough to enable detection of possible efficacy: their symptom scores of asthma had to be higher than 3 (out of 5) on 4 days a week prior to randomization; the requirement for the bronchodilator Proventil had to exceed 4 puffs per day on 4 days out of 7; FEV_1, the volume that can be expired in one second, had to be reduced to values between 45–85% of predicted values with at least 15% reversibility.

After a 1- to 2-week single blind placebo washout phase, during which the patients were withdrawn from their regular asthma medication, patients were randomized and treated blind with 900 μg or 3000 μg of nebulized Icatibant or placebo. Treatment was for 4 weeks, followed by a 2-week placebo run-out.

The medication was nebulized three times daily with a conventional nebulizer (PARI-LC-JET Plus). Concomitant medication was not allowed except for rescue medication with Proventil MDI, a bronchodilator beta agonist. Up to 12 puffs a day were allowed if needed.

The primary efficacy variable was the subject's asthma symptom severity evaluation. Patients recorded in their diary separate global scores for daytime (limitation of daily activities) and nighttime asthma symptoms (disturbed sleep). Symptoms including wheezing, cough, chest tightness and/or shortness of breath were rated according to a 6-point scale with no distinction of individual symptoms.

Secondary efficacy variables included pulmonary function tests (PFTs) measured by investigator (FEV_1, PEFR, FVC, FEF(25–75%) at weekly scheduled visits, patient's global evaluation of efficacy and tolerability, investigator's global evaluation of efficacy, patient's PEFR measurements (morning: prior and 15 min after dose, evening: prior and 15 min after dose), number of patients using Proventil MDI as rescue medication and the average daily puffs used by each patient during the trial, withdrawal due to drug failure and emergency room visits and/or hospitalization because of asthma. Safety variables included standard clinical and laboratory safety parameters.

To answer the question whether Icatibant exhibits bronchodilator action in a subgroup of 30 patients spirometric measurements were performed before and at regular intervals up to 7 h after inhalation of the morning dose of Icatibant at day one (first dose) and repeated at 3 and 4 weeks.

3. Results

Patients enrolment: 84 to 87 patients were evaluated for efficacy (intent-to-treat) in each treatment

Table 1
Average daily use of Proventil MDI

	Mean puffs						
	Baseline	Week 1	Week 2	Week 3	Week 4	RO Wk 1	RO Wk 2
Placebo	5.7	0.5	6.2	6.1	5.8	5.7	5.2
900	6.5	0.5	6.5	6.6	5.9	5.5	4.8
3000	6.5	0.3	5.7	5.8	5.8	5.3	4.8

Week 1–4: weeks of active treatment.
RO Wk: week of placebo run-out phase.

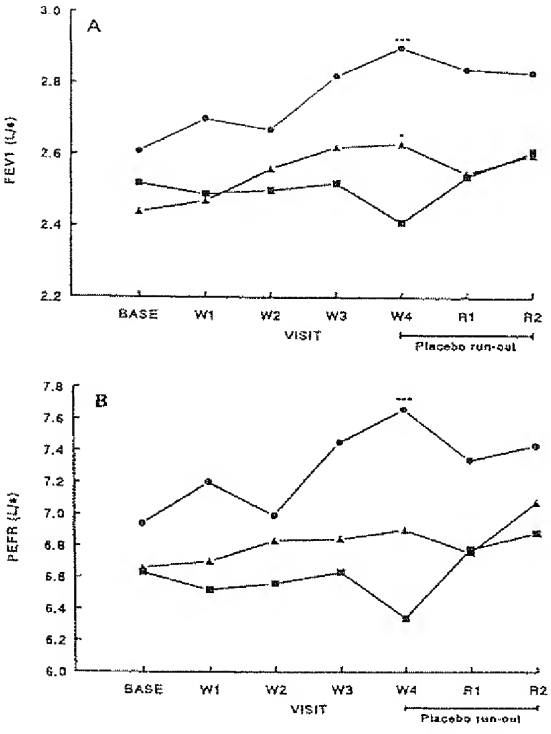

Fig. 1. Pulmonary function tests measured by the investigators at weekly intervalls before, during the active treatment with Icatibant and placebo run-out phase. (A) Forced expiratory volume (FEV_1). (B) Peak expiratory flow rate (PEFR). Placebo (squares), Icatibant 900 μg (triangles) and Icatibant 3000 μg (circles). * $p < 0.05$, *** $p < 0.01$ compared with placebo (adjusted on baseline).

group. Icatibant was very well tolerated and there were no serious adverse events which could be attributed to Icatibant. Four weeks treatment led to a dose-dependent improvement in objective pulmonary function tests (PFTs) measured by the investigators (e.g. FEV_1 and PEFR, Fig. 1). At 3 mg t.i.d., a statistically significant difference ($p < 0.001$) between Icatibant and placebo of about 10% (change from baseline) was detected after 4 weeks of treatment for all PFTs. At the lower dose of 900 μg t.i.d., the improvement in PFTs was smaller and significant between treatments ($p < 0.05$) for only FEV_1 and FEFR (25–75%). The improvement in objective PFTs started between week one and two, gradually increased and was still tending upwards at the end of the active treatment, and slowly decreased

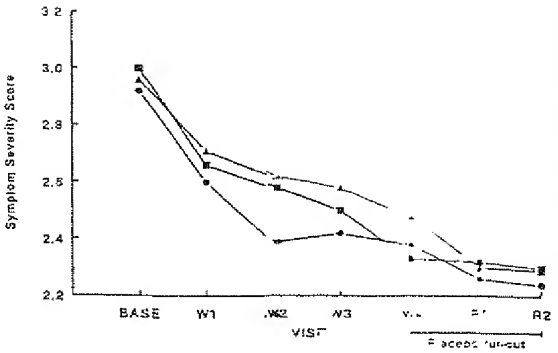

Fig. 2. Symptom severity score from patient[illegible] during the active treatment with Icatibant and placebo run-out phase. Average of day- and nighttime symptoms (Placebo squares), Icatibant 900 μg (triangles) and Icatibant 30[illegible].

during a two-week placebo run-out p[illegible]. In contrast to the improvement in objective PFT[illegible] there was no improvement over placebo on the following variables: global symptom score (Fig [illegible]), the use of rescue medication (Table 1), patient [illegible] and investigator's global evaluation of efficacy a[illegible]. No significant difference between treatments in [illegible] PEFR measurements although a trend t[illegible] improvement could be found.

Spirometric measurements made [illegible] up to 7 h after the morning dose at day [illegible] (first dose), week 3 and 4 showed no acute bron[illegible] activity of Icatibant. Fig. 3 shows the [illegible] placebo and the two doses of Icatibant on [illegible] placebo,

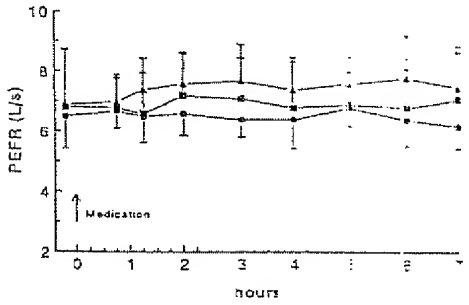

Fig. 3. PEFR measurements by the investig[illegible] h after inhalation of Icatibant on the first study day [illegible] investigation of a possible broncodilator effect of Icatib[illegible]. Mean ± S.E.M., $n = 10$/group. Placebo (squares), Icatibant [illegible] es) and Icatibant 3000 μg (circles).

900 and 3000 μg of Icatibant on day 1 of treatment (first dose).

4. Discussion

The study was well designed with a large number of patients, and the patients were of sufficient severity. Icatibant led to a dose-dependent improvement in objective pulmonary function tests (PFTs) determined by the investigator like FEV_1 and PEFR. In contrast to the improvement in objective PFTs, no clinically relevant improvement in subjective parameters was found.

From the time course of the improvement of the objective PFTs measured by the investigators, we assume that the effect of Icatibant is anti-inflammatory in line with the idea that inflammation needs time to resolve. The objective PFTs started to improve with delay, gradually increased until the end of active treatment with no indication of a plateau suggesting that the maximum effect had not yet been achieved. The slow decrease of these values during the placebo run-out phase supports the assumption of an anti-inflammatory mechanism.

An acute bronchodilator effect could not be found during the 7 h of observation after acute inhalation excluding a major bronchoconstrictor role of bradykinin in asthma in these patients. BK given exogenously as a potent bronchoconstrictor in asthmatics and animals. As suggested by the failure of Icatibant to cause significant bronchodilation in this study endogenous BK is not a major bronchoconstrictor in this population of asthmatics. Even in the first hour after inhalation when drug levels in the bronchi are still highest, no bronchodilator effect was seen.

In sensitized guinea pigs Icatibant showed a moderate but significant inhibition of ovalbumin-induced bronchoconstriction. In the presence of the neutral peptidase inhibitor phosphormidon the inhibitory effect was more pronounced (Ricciardolo et al., 1994).

The discrepancy between induction of bronchoconstriction by exogenous BK and the failure of Icatibant to cause significant bronchodilatation in these asthma patients may be explained by the possibility that endogenous BK concentrations occurring in the bronchi in asthma are lower than concentrations reached with exogenous BK, probably too low to elicit bronchoconstriction. In isolated human bronchi BK is a poor bronchoconstrictor. The bronchoconstrictor effect of BK is most likely not due to a direct effect on bronchial smooth muscles but rather a neurally mediated effect by stimulation of sensory nerve endings of C-nerve fibres (Kaufman et al., 1980; Fuller et al., 1987; Miura et al., 1994). A second possibility is that these complex bronchoconstrictor mechanisms become desensitised in the continuous presence of endogenous BK. The latter idea, however, is difficult to reconcile with the high sensitivity of asthmatics against inhaled bradykinin.

These considerations on the bronchoconstrictor role of BK obviously do not apply to the presumed inflammatory role of BK. BK is one of the most potent inflammatory compounds with a plethora of different mechanisms related to inflammation (Bhoola et al., 1992). Our data with Icatibant seem to confirm the inflammatory nature of endogenous BK in human asthma. The precise mechanisms remain to be determined. A major mechanism could be the stimulation of plasma exudation (Sakamoto et al., 1992; Bertrand et al., 1993; Nakajima et al., 1994). Interestingly, exuded plasma is the source of the (plasma) precursors of BK.

For several reasons the full clinical potential of Icatibant may not have come to light in this short-term pilot study. From the fact that the improvement in objective PFTs has not yet reached a plateau after the end of active treatment a further improvement of PFTs can be expected that will finally lead to an improvement in clinical symptoms. Moreover, the conditions of this pilot study were certainly sub-optimal with relatively long times required for three times daily inhalations with a nebuliser. A further disadvantage was the use of a global symptom score which did not allow distinction between individual symptoms like wheezing, chest tightness and/or shortness of breath and cough. It would have been particularly interesting to find out whether Icatibant has an effect on cough, as bradykinin causes cough and the antagonist shows some efficacy in animal models of cough.

In conclusion, Icatibant was well tolerated and showed a profile expected for an anti-inflammatory asthma drug. The data with Icatibant show that BK plays a role in human asthma but they exclude a

major role as a bronchoconstrictor in our asthma population. Whether antagonism of BK can become an appropriate treatment for asthma remains to be determined in future clinical studies.

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